REMARKS/ARGUMENTS

By this Amendment, claims 8 and 66 are canceled, claims 3, 62, and 76 are amended. Claims 14, and 48-50 have been withdrawn from consideration pursuant to a restriction requirement. Claims 3, 5-7, 9-14, 48-65, and 67-86 are pending.

Support for the amendments to the claims can be found throughout the Specification as filed, and specifically in original claim 8.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection Under 35 U.S.C. § 102(b)

Claims 3, 5-13, 51-56, 59, 62-71, 76-81, 84 stand newly rejected under 35 U.S.C. 102(b) as being anticipated by Clarke et al., 2000, Science, 288: 1660-1663. This rejection is respectfully traversed.

The Examiner argues that Clarke et al. teach isolation of a neural stem cell from the adult mouse brain and that it can give rise to cells of all germ layers (citing Clarke et al., abstract). The Examiner argues that with regard to the cells being a purified culture (i.e., a composition consisting of isolated stem cells), Clarke et al. teach that clonal cultures were established (citing Clarke et al., page 1661, 2nd col., 2nd parag.). The Examiner argues that while the instant claims recite a source of the claimed cells, the source provides no structural characteristic that distinguishes stem cells from the brain from stem cells from gastrointestinal tissue and thus, according to the Examiner, as far as can be told, Clarke et al.'s cells anticipate the claimed invention. (Office Action at page 4).

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Clarke et al. reference.

The instant claims are directed to a composition consisting of isolated pluripotent adult stem cells obtained from an exocrine glandular tissue of a salivary gland, a lacrimal gland, a sudoriferous gland, a sebaceous gland and/or gastrointestinal tissue, wherein the exocrine glandular tissue originates from a mammal, and further wherein the isolated pluripotent adult

stem cells are capable of differentiating into cell types of all three germ layers in a culture medium that does not contain any additional growth factors or differentiation factors after culturing under spatial conditions which ensure three dimensional contact of the cells.

However, here the newly cited reference Clarke et al. actually discloses adult (neural) stem cells with pluripotent characteristics. Contrary to the cells of the present invention, however, pluripotency, i.e. the capability to differentiate into cells of all three germ layers, appears to be dependent from an activation or induction in a suitable environment.

For Example, Clarke teaches that (Clarke at page 1660):

> We reasoned that inductive signals for differentiation to diverse lineages must be present in these cultures. To evaluate the capacity of inductive signals from ES cells to guide the differentiation of neural stem cells, we cultured adult neural stem cells together with embryoid bodies

Additionally, the Clarke references teaches that (Clarke at page 1661):

> To analyze the differentiation potential of adult neural stem cells in vivo, we assayed their ability to contribute to the formation of various tissues by introducing them into the early embryonic environment and observing the fate of their progeny.

Thus, the adult stem cells of Clarke et al. are either co-cultivated with embryonic stem cells/embryoid bodies which are expected to affect the adult stem cells by releasing specific signals and/or growth and differentiation factors and which co-culturing also offers the possibility of cell fusions and transfer of pluripotent features from embryonic to adult stem cells or to hybrid cells or which cells are implanted into chick and mouse embryos which also provide an inductive environment due to the presence of specific growth and differentiation factors in the tissues of said embryos (see e.g. page 1661, first column, second paragraph: "These cells would then be exposed to various inductive environments in the different germ layers.").

Clarke et al. do not disclose any spontaneous differentiation of the stem cells in a simple cell culture medium without additional growth and differentiation factors as observed with the adult stem cells of the present invention which are derived from exocrine glandular tissue. Said capability to spontaneous differentiation represents a very advantageous feature of the present cells, which could not be expected by the skilled artisan.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 3, 5-13, 51-71, 76-86 stand newly rejected under 35 U.S.C. 103(a) as being unpatentable over Zulewski et al., Apte et al., Pittenger et al. This rejection is respectfully traversed.

The Examiner argues that Zulewski et al. teach that nestin-positive cells are in localized regions of the ducts in exocrine acinar tissue in the rat pancreas and that nestin positive cells are mostly devoid of staining for CK19 (a marker of ductal epithelium). The Examiner argues that Zulewski et al. teach that nestin-positive cells in pancreatic ducts and represent stem cells that have not yet differentiated into a ductal or endocrine phenotype (citing Figure 6).

While the Examiner sets forth that Zulewski et al. teach the identification of nestin-positive cells in ductal cells in acinar tissue of rats, the Examiner admits that Zulewski does not teach that clonal lines were made of the cells.

The Examiner argues that Apte et al. teach how to obtain cells from the acini of pancreas. The Examiner argues that with regard to obtaining a single cell from a mixture of cells, Pittenger et al. provides this guidance by teaching that fibroblastic cells that developed into visible symmetric colonies 5-7 days after initial plating and that hematopoietic stem cells (HSCs) and nonadherent cells were removed with changes in medium

The Examiner argues that all of the component parts are taught in the combination of Zulewski et al., Apte et al., and Pittenger et al. The Examiner alleges that the only difference is the combination of the "old elements" such that a line of stem cells from pancreatic acinar tissue is obtained. The Examiner argues that it would have been obvious to an ordinary artisan to make a cell line of the nestin-positive cells in pancreatic acini because Zulewski et al. teach that these cells are stem cells.

The claims are patentable over the combination of the Zulewski et al., Apte et al., and Pittenger et al., references for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the

scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)).

Here, the claims are directed to a composition consisting of isolated pluripotent adult stem cells obtained from an exocrine glandular tissue of a salivary gland, a lacrimal gland, a sudoriferous gland, a sebaceous gland and/or gastrointestinal tissue, wherein the exocrine glandular tissue originates from a mammal, and further wherein the isolated pluripotent adult stem cells are capable of differentiating into cell types of all three germ layers in a culture medium that does not contain any additional growth factors or differentiation factors after culturing under spatial conditions which ensure three dimensional contact of the cells. Thus, the claims are directed to providing pluripotent adult stem cells, i.e. cells having the capability to differentiate into cells of all three germ layers.

The Examiner asserts that the presence of "nestin-positive cells", which appears to be used as a synonym to "pluripotent cells", is disclosed in Zulewski et al., a method to obtain cells from the acini of pancreas is taught by Apte et al. and a method for obtaining single cells from a mixture of cells is disclosed in Pittenger et al. Actually, however, the article of Zulewski et al., which has been published in 2001, describes nestin as a neural cell-specific stem cell marker (see e.g. abstract of the Zulewski reference) and the isolated cells disclosed in Zulewski are merely multi-potent in as far as they are capable to differentiate into different pancreatic endocrine, exocrine and hepatic phenotypes, not pluripotent cells.

However, as evident for the skilled artisan, all those cell types are derived from a single germ layer, namely the endoderm. Furthermore, the identification of nestin as a marker expressed by pluripotent stem cells (which previously has been queried by the Examiner) is based on the article published by Wiese et al. (CMLS 61 (2004, 2510-2522; cited on the IDS submitted 06/26/2009 and discussed in the Response filed 06/26/2009) in the second half of

2004, i.e. well past both the priority date and the international filing date of the present application. Consequently, at the date of the present invention the skilled artisan did not get any hint from Zuleswki et al. - which describe nestin-positive but merely multi-potent stem cells - that true pluripotent adult stem cells may be obtained from pancreas and other exocrine glandular tissue by using a specific isolation and cultivation method not described therein.

The disclosure of Pittenger et al. relates to the cultivation of mesenchymal stem cells and their capability to differentiate into several cell types derived from a single germ layer, namely the mesoderm. For example, the Pittenger reference teaches that (Pittenger at page):

> We characterized homogeneous human mesenchymal cells from bone marrow taken from the iliac crest (5) (see Web Fig 1, available at www. sciencemag.org/feature/data/983855.shl). Previous studies have identi1ied selection criteria for fetal bovine serum (FBS) that allows the expansion of a marrow cell population with MSC potential after implantation (5, 1 J). 11ie mesenchymal cells described here were characterized by their ability to proliferate in culture with an attached well-spread morphology (Fig. 1, A and B), by the presence of a consistent set of marker proteins on their surface (Fig. 1, C and D) (12--14), and by their extensive consistent differentiation to multiple mesenchymal lineages under controlled in vitro conditions (Fig. 2).

Apte et al. also do not teach the isolation of pluripotent or even multi-potent adult stem cells. For example, the Apte reference teaches (Apte at page 137):

> Using immunohistochemical methods, this study has provided evidence that the rat pancreas contains cells which exhibit features similar to those described for hepatic stellate cells. The number of these stellate shaped cell in rat pancreas was comparable to that of stellate cells in the liver. Furthermore, the study has shown, for the fist tie, that these cell can be isolated from the pancreas and cultured in vitro.

Thus, even a combination of all three documents did not provide the skilled artisan attempting to isolate pluripotent adult stem cells with any incentive to use the source material and the method of this application in order to arrive at the solution of the present invention.

Therefore, since the combination does not teach or suggest all the claim limitations, and therefore, since the combination of the patents does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no reasonable expectation of success.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

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By_____

Joseph F. Murphy
Registration No. 58,313
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.